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Some of the Products in Article on New Medicinal Agents

(see page 343)

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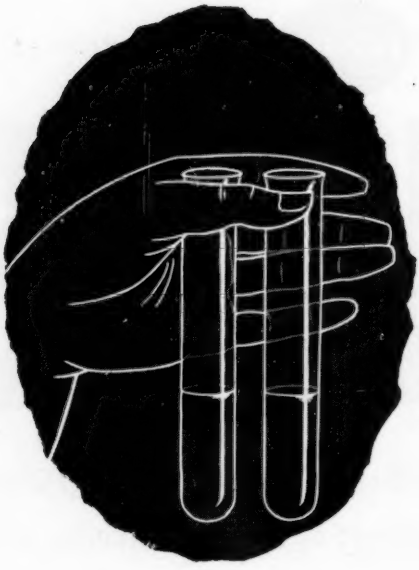

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AND THE SCIENCES SUPPORTING PUBLIC HEALTH

Since 1825

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EDITORIAL

MEDICAL PROGRESS AND THE FUTURE

THIS issue contains a review of the progress made in the development of new medicinals during recent months. So accustomed have we become to the advent of new and remarkable therapeutic agents that one is likely to take for granted many of these really important advances.

It is not difficult for us, however, to recall the weakness of therapeutics only two decades ago when many diseases were treated symptomatically with little or no assistance rendered the body's defense or regulatory mechanisms. Today highly specific drugs are available for many conditions. Anti-infectives are now commonplace which twenty years ago would have been classed as the products of the most vivid imagination and found only in the comic strip. The hormones which govern life's most intricate mechanisms are now in many cases made synthetically, and in a few instances synthetic derivatives exceeding the potency of natural products are prepared.

Twenty years ago little data were published on the vitamins, and cod liver oil was almost the only vitamin-containing substance commonly used; even so, its vitamin content was considered as only of secondary importance.

Today we have analgesics superior to morphine, antimalarials that have all but displaced quinine, digitalis principles that are as potent and rapid when given orally as intravenously, sympathomimetics, parasympathomimetics, nerve-blocking agents and a complex array of highly specific substances that make the alteration of body function possible.

With dimercaptopropanol we can *reverse* the heretofore irreversible tissue-arsenic complex. Absorbable sponges of fibrin and gelatin make brain surgery safer through hemorrhage control. Shock is combatted with serum albumin or gelatin together with adrenal cortical hormones. Babies who until recently were certain to die with *erythroblastosis fœtalis* now are sometimes saved by transfusion since we know the significance of the Rh factor. Pregnancies that formerly would have consistently resulted in miscarriage are now

brought to term with progesterone. And so we might continue, for the list is endless.

What is left to be done and what shall be the eventual outcome? The first part of this question can be answered on the basis of fact; the second can only be a blend of clairvoyance and philosophy, fields in which the amateur may perchance some day prove to have been wiser and more prophetic than the acknowledged expert.

The most important diseases left for which we need a good therapeutic approach are as follows:

Tuberculosis—This is an old offender and one for which some satisfactory chemotherapy is still sought. With world-wide malnutrition now prevalent it may well become a serious problem. Streptomycin has offered some promise in early tuberculosis, and it is somewhat more effective in combination with promin and chaulmoogra oil.

Cancer—With the children's diseases now fairly well controlled, more people grow old and geriatrics replaces pediatrics in importance. Cancer, although not confined to old persons, is more common in the higher age brackets and ranks just under cardiovascular disease as a cause of death. So far, we know how to identify cancerous tissue and how to destroy it, providing it is not too intimately connected to other vital tissues. Whether surgery, X-rays, radium, or other radioactive elements are used is a matter of choice. The real problem of cancer is its etiology. Many substances are known which cause cancer, but the reason why normal tissue crosses the boundary and becomes cancerous is unknown. The answer to this enigma surely lies in learning more of cell physiology, since until its normal physiology is understood abnormal physiology cannot be explained. Tracer elements may prove a great help to the physiologist and it is in this direction that success must lie. There is, of course, always the chance of a solution of the problem by sheer luck without the missing links being supplied. This has happened in other directions and it could happen again.

Virus Diseases—The virus diseases are the most discouraging to the research worker. Lying between non-living protein and the bacteria, the viruses seem to be a class buy themselves. Consider the common cold and poliomyelitis and the complexity of this field is immediately evident. The use of the chorio-allantoic membrane

of chick embryos as a culture medium was a great forward step which has made virus culture in some cases quite easy. Much is now known about virus diseases but some still are without effective control measures.

Cardiovascular diseases—These represent the number one problem of all, since they are the cause of most deaths each year in the United States. Drugs which ameliorate the diseased state of the tissues are of course widely used, e. g., digitalis, vasodilators, etc., but this is palliative treatment only. What is the basic physiological explanation for the fact that some men's arteries are older at 45 than others at 70? That infection plays a part is known. It is also believed that the diet and even the emotional state influence this condition, but no clear picture of the final factors causing arteriosclerosis is available. In all likelihood a solution of this problem involves the problem of aging itself, but this should not discourage the investigator for this too shall some day be subject to considerable control.

Today biochemists are beginning to understand something of the enzyme systems functioning in cell physiology, and a very complex system it is. This is but a beginning but a more basic and important field of research cannot be imagined. Cytochrome C is the first medicinal product resulting from this study, and others will undoubtedly follow.

Providing man makes sufficient social and political progress that he sees the folly of self-destruction by atomic warfare before this happens, and providing man's artificial environment which he has created does not make him a psychosomatic casualty beforehand, there is every reason to believe that all diseases may someday be conquered. The process of aging will be slowed more and more and man will live a longer and longer time, barring some unforeseen genetic accident.

If by this time man has not retrogressed through exhaustive wars and world chaos, many changes will of necessity have been made. There will be no barriers of nationalism, color or creed. The population of the world will have been brought into balance with its optimum productivity by birth control, and man will live as an adjusted social being free of all want and fear and in control of his own destiny.

L. F. Tice.

CURRENT TRENDS IN NEW MEDICINAL AGENTS

By Madeline O. Holland, D. Sc.

RESEARCH leading to the development of new medicinal agents has never been more intensive than over the past few years. The impetus given research during the war years did not cease with the end of hostilities nor is it likely to. The widespread acceptance and demand for new specifics by the medical profession speaks favorably for the painstaking labor of those chemists, pharmacologists and pharmacists who have made these new substances possible.

In this review of new therapeutic agents an attempt has been made to present a brief description of many of these new products. Some are already available on the market; others are being tried experimentally and may or may not be released depending upon the clinical results obtained.

It is interesting to note that, although synthetic medicinals still lead in numbers, many products of animal or vegetable origin are of great importance. Synthetic medicinals undoubtedly offer the ultimate in purity, predictability and simplicity of control, but as yet many natural products remain unsynthesized and may so remain indefinitely.

No attempt has been made in the following review to arrange the several drugs in the order of their relative importance. Those having a somewhat related pharmacological action are in most cases grouped together.

Enterogastrone

Peptic ulcer in humans has been a medical problem for many years. Perforation or hemorrhage in untreated or unsuccessfully treated cases has resulted in death to many. Emotional disturbances have been shown to bear a relationship to peptic ulcer and this factor should not be overlooked in the therapy. However it is also necessary to use the proper drugs. Many substances have been tried, some with some measure of success, others with total failure.

Since the discovery of secretin in 1902 the gastrointestinal autocoids have attracted the interest of physiologists as possible therapeutic agents. Histamine, secretin and cholecystokinin have shown value as diagnostic aids but enterogastrone is the only one to show

therapeutic value. It has been isolated from the mucous lining of the upper intestinal tract of freshly slaughtered hogs. The name is derived from the three words enteron, gastron and chalone. It is believed to act by inhibiting gastric secretion.

Experiments with enterogastrone on dogs with ulcers revealed complete healing of the ulcers and when treatment was stopped no recurrences took place for at least 18 months.

Following the animal experiments enterogastrone was next tried on humans. Selected for the study were ulcer patients who had been suffering with the condition for at least five years. The dose calculated as preferable was 100 to 1000 mg. but due to expense of extraction a daily dose of 200 mg. was selected. In some cases it was necessary to reduce the preliminary dose to 100 mg. due to pain at the site of injection. Definite improvement verified by X-ray was noted in most cases in a period of two to five months. Some gained weight and were able once more to live on a normal diet. Treatment was discontinued within six months to a year and none who had received six injections a week for six months showed any signs of recurrence. Enterogastrone thus may prove to be the drug for preventing recurrences in peptic ulcer. It is available for clinical trial only.

Resin Antacid

The discovery in 1935 that some resins take up hydrochloric acid opened a new field in the therapy of gastric acidity. The use of the synthetic resin group of ion-exchange chemicals suggested the possibility that the principle might be applied in controlling pH of the gastrointestinal tract secretions.

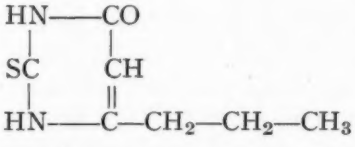
Resinat or resin antacid is such a product. It is a yellow, tasteless powder available in capsule form. Chemically it is a polyethylene-polyamino methylene substituted resin of diphenyloldimethylmethane and formaldehyde in basic form. It is purified and ground to a particle size of about 200 mesh so as to give it sufficient surface area to enhance its acid-adsorbing qualities. Resinat acts by attracting to itself the excess hydrochloric acid of the stomach and after so doing passes into the intestine where the alkalinity causes it to drop the acid molecules which are absorbed. The resin is eliminated unchanged and without having had any effect on the gastrointestinal tract.

Resinat is rapid in action and possesses great acid normalizing power and a specific capacity to inhibit pepsin activity. It controls the symptoms of gastric hyperacidity without eructation, is nonconstipating, nontoxic and nonirritating, and does not disturb the acid-base balance of the body fluids. It is effective in the therapy of peptic and duodenal ulcers.

Resinat is supplied in capsules containing 0.25 Gm. in each by The National Drug Co. The dosage recommended in ordinary hyperacidity is one or two capsules with a few sips of water and repeated as required. In acute peptic and duodenal ulcers one or two capsules should be given every two hours during the day. Dietary restrictions are also necessary.

Thiouracils

About three years ago thiouracil was introduced into medicine as a therapeutic agent in hyperthyroidism. More recently a derivative of this drug has been made available. Known as propylthiouracil or 6-*n*-propylthiouracil it is a white crystalline substance with a bitter taste and has the following structure:



Propylthiouracil is used preoperatively for thyroidectomy or as a substitute for thyroidectomy. It reduces the basal metabolic rate to a normal level. The period of preoperative preparation can be prolonged for a sufficient length of time to allow the patient to recover from the adverse effects of the hyperthyroid condition, making the patient a better operative risk. By thus controlling the patient preoperatively the postoperative course is not so severe. In cases where an operation is contraindicated thiouracil has been used effectively to control the condition for several months and it is expected that propylthiouracil will do likewise. However the clinical data available on remissions is not sufficient to indicate that these drugs be used instead of surgery in patients who are considered good surgical risks.

The thiouracils are contraindicated during pregnancy and lactation since thiouracil has been shown to pass through the placental

barrier and inhibit the thyroid function of the fetus. Examination of milk from women who have taken the drug during lactation showed significant quantities present. Such studies for propylthiouracil have not been reported but it can be assumed to be so from the similarity of other actions unless proven otherwise. Propylthiouracil shows less incidence of side-effects and untoward reactions than does thiouracil. Patients who have shown reactions with the latter have taken the propyl compound without difficulty. It has also shown value in patients showing intolerance to iodine therapy. The incidence of agranulocytosis is also less with the propyl derivative.

If agranulocytosis does occur the drug should be stopped immediately and 1,000,000 units or more of penicillin administered daily in divided doses until the white count becomes normal. Sulfonamides and coal-tar derivatives should be avoided. Transfusions of 250 to 300 cc. of fresh whole blood should be given every four to six hours.

Propylthiouracil is administered orally in doses of 100 to 150 mg. daily. The total dose should be divided into four and given every six hours. Larger doses may be necessary but should not exceed 250 mg.

Propylthiouracil is supplied in tablet form by Eli Lilly and Co., Abbott Laboratories, Lederle Laboratories and others.

Several other derivatives of thiouracil are under investigation but have not been released at present. They include 6-methylthiouracil, cyclopropylthiouracil and cyclohexylmethylthiouracil. The two latter compounds are more active than thiouracil but less so than is propylthiouracil. Cyclohexylmethylthiouracil is thought to have a greater therapeutic index than thiouracil, propylthiouracil and cyclopropylthiouracil.

BCG Vaccine

BCG is the commonly used abbreviation for Bacillus Calmette-Guérin. From this bacillus is made a vaccine which has met with some success in immunization against tuberculosis. It was first made available in France in 1924. It is today accepted by the medical profession and laymen in the Scandinavian countries and in certain Latin American countries as an important adjuvant to established measures against tuberculosis. However in the United States its use is strictly controlled. An institution for tuberculosis prevention is

being erected at the University of Illinois in Chicago where the entire supply will be manufactured.

Although this vaccine does not eliminate tuberculosis it provides a definite advance toward its eventual eradication. It is harmless to humans and provides partial immunity against tuberculosis. Both adults and children to whom it has been given are not so susceptible to the disease. The immunity lasts for about five to seven years.

Use of this vaccine does not eliminate the need for standard measures such as mass X-ray examinations and tuberculin surveys for the detection of the condition and prevention of dissemination of the bacilli by isolation and treatment of actual cases. The vaccine is administered intracutaneously or transcutaneously. With the latter method the possibility of formation of local abscesses is eliminated.

Hydrogen Peroxide Glycerite

Glycerite of Hydrogen Peroxide is a new antiseptic solution for topical application which has shown results in the therapy of postoperative incisions, wounds and lacerations, cysts and abscesses, varicose and diabetic ulcers, impetigo, herpes simplex, fissure of the lip, anorectal fissures, tuberculous abscesses, tinea of hands and external ear, pyogenic infection of tissues lateral to the fingernail, fungus disease of the nails of the fingers and toes, eroded lesions of the interdigital webs of the hands and feet, dermatophytosis, Vincent's angina, postoperative and postextractive oral infections, lingual tonsillitis and aphthous stomatitis. Supplied as a solution it contains 2% each of hydrogen peroxide and 8-hydroxyquinoline in a specially prepared glycerol. It is stable, anhydrous, deodorizing, hemostatic, nontoxic, detergent, nonallergenic and nonirritating; as it reacts it evolves active oxygen. Laboratory studies have established that Glycerite of Hydrogen Peroxide is bactericidal for gram-positive and gram-negative organisms as exemplified by *Staphylococcus aureus* (FDA 209), streptococci (alpha and beta hemolytic), an enterococcus, *Micrococcus epidermidis, Pseudomonas aeruginosa, Escherichia coli, Aerobacter aerogenes,* and *Eberthella typhosa,* and bacteriostatic for diphtheroids.

Glycerite of Hydrogen Peroxide with Carbamide contains 1.44 per cent of hydrogen peroxide, 2.55 per cent of urea, and 0.1 per cent of 8-hydroxyquinoline in anhydrous glycerol and is indicated

in otitis media and otitis externa. Both products are marketed by the International Pharmaceutical Corp.

Dibromsalicylaldehyde

Dibromsalicylaldehyde has been found to be effective in the treatment of chronic infections of the ear caused by gram-negative organisms and in particular against *Pseudomonas aeruginosa* (pyocyaneous) infections. It is also effective against gram-positive organisms and is fungicidal as well. Thus it is indicated in the treatment of epidermophytosis and in chronic suppurative otitis media and external otitis. The drug is available in the form of the solution, ointment and dusting powder under the trade-name of Dalyde and is supplied by Hynson, Westcott and Dunning.

Salicylanilide

One of the most resistant dermatoses which attacks school children is *tinea capitis* or ringworm of the scalp. Salicylanilide has been shown to be effective in treating this condition. This discovery resulted from the use of this compound against the molds and fungi which attacked the equipment of our fighting men in tropical climates. Thus far it has surpassed all other measures employed in treating *tinea capitis*. Salicylanilide is supplied with the germicide Phemerol in a water-miscible base as Salicylanilide-Phemerol Cream by Parke, Davis and Co. and alone in a strength of 4.5 per cent in a special base as Ansadol Ointment by William H. Rorer, Inc.

Tubocurarine Chloride

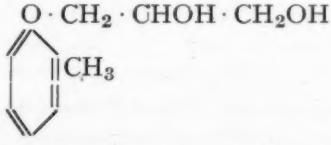
Curare has been available in the United States under the trade name of Intocostrin for some time. Recently the principal active constitutent of this drug has been isolated. It is an alkaloid and is known as *d*-tubocurarine. When injected intravenously in the form of the chloride it rapidly causes paralysis of the skeletal muscles without embarrassment of respiration until later since the diaphragm and intercostals are the last to be influenced. The maximum effect is quickly reached and lasts for only a short time since the drug disappears rather rapidly from the bloodstream. Tubocurarine chloride is indicated in surgery to secure muscular relaxation; in shock therapy of mental conditions to soften the convulsions; in the relief

of spastic and athetoid states; as a diagnostic agent in myasthenia gravis; and in certain manipulative procedures as a relaxant.

Tubocurarine is available as the chloride in a sterile isotonic aqueous solution for parenteral administration standarized to contain 2.7 mg. of the anhydrous crystalline alkaloid per 1 cc. and is marked as Solution Tubocurarine Chloride by E. R. Squibb and Sons. It can be used interchangeably with Intocostrin. Each cc. contains an amount equivalent to 20 units of the latter. Abbott Laboratories have available *d*-Tubocurarine Chloride in buffered isotonic solution of which each cc. represents 3 mg. of *d*-tubocurarine chloride pentahydrate, 1 mg. of sodium metabisulfite and 0.9 per cent of benzyl alcohol (preservative). A statement has been made that 2.7 mg. of the anhydrous alkaloidal salt are the equivalent of 3 mg. of the pentahydrate.

Myanesin

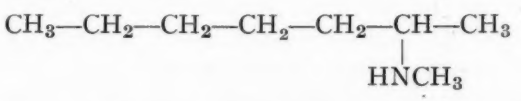
Although Curare is employed to relax the muscles during light anethesia there is some danger in doing this since the quantity of curare necessary is close to that which will cause paralysis of the diaphragm. A new compound discovered in Britain has been found to cause muscular relaxation and paralysis without embarrassment of respiration. Chemically it is known as α-β-dihydroxy-γ-(2 methyl-phenoxy)-propane and has been given the tentative trade-name of Myanesin. Its chemical structure is:



It is a colorless, odorless crystalline solid. Myanesin possesses a potentiating effect on barbiturate anesthesia. It does not act on the brain and its action definitely differs from that of curare. It possesses a greater margin of safety than does curare. Under pentothal-N_2O-O_2 anesthesia Myanesin produces abdominal relaxation so easily that it eliminates the need for the more toxic cyclopropane. However this drug should be used only by expert anesthetists. It is available from The British Drug Houses Ltd. of England and Canada.

Oenethyl

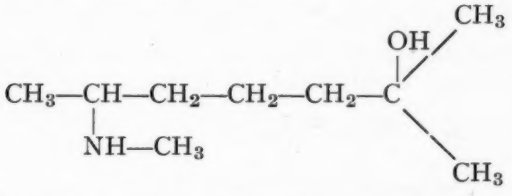
Oenethyl chemically is 2-methylamino-heptane, an aliphatic amine with the structural formula:



It is a clear, colorless volatile fluid, slightly soluble in water but with acids forms salts which are readily soluble in water. It has a vasopressor action similar to that of the aromatic amines but its effect is sustained over a longer period of time than that of epinephrine. It is useful in treating the hypotension often associated with spinal anesthesia. It does not produce a dramatic rise in blood pressure as do epinephrine and neosynephrine. It is supplied by Bilhuber-Knoll Corp. as a 5 per cent aqueous solution of the hydrochloride in ampuls of 1 cc. which contain 50 mg. of drug.

EA 83

A new synthetic vasopressor drug known as EA 83 has been described. Chemically it is 2-methylamino-6-hydroxy-6-methyl-heptane or 2-methylamino iso-octanol.



It is chemically related to Tuamine, Oenethyl and Octin. It shows promise as a strong heart and circulatory stimulant in cases of circulatory collapse. It may be useful in many of the usual conditions in which sympathomimetics are effective. Among these are included shock, general allergic conditions, angioneurotic edema, asthma and urticaria.

Oralator

A new and revolutionary therapeutic principle in the control of cough has recently been developed. It consists of the topical application of an anesthetic-analgesic compound in vapor phase. Symptomatic relief of non-productive cough is achieved in a few seconds

by inhaling as a vapor, 2-amino-6-methylheptane. It is indicated in coughs due to colds and inflammatory conditions of the respiratory system such as laryngitis, pharyngitis, tracheitis, laryngo-tracheitis and acute tracheo-bronchitis. It has also shown value in some coughs in bronchial asthma. By inhaling the vapor from the special Oralator the drug is carried directly to the principal zone where the cough reflex originates. Since it possesses negligible pressor effects and no central nervous stimulation in therapeutic dosage, the margin of safety is wide. It is not recommended for children under seven years of age due to the difficulty children have in inhaling. Each Oralator contains 350 mg. of the drug and aromatics. It is available from Smith, Kline and French Laboratories.

Metopon

Metopon is the name given to the hydrochloride of methyldihydromorphinone. This compound is the result of a study of drug addiction started in 1929 by the National Research Council with the object in view of finding a non-addicting analgesic comparable to morphine.

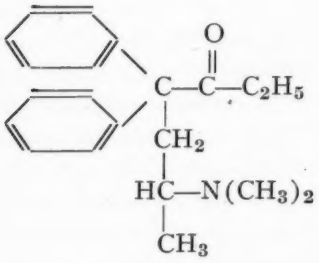
Pharmacologically methyldihydromorphinone hydrochloride is qualitatively like morphine even to the properties of tolerance and addiction but quantitatively it is different in all of the major actions. Its analgesic action is at least double and its duration of action is about equal to that of morphine; it is nearly devoid of emetic action; tolerance to it appears to develop more slowly and to disappear more quickly, and physical dependence builds up more slowly than with morphine; therapeutic analgesic doses produce little or no respiratory depression and much less mental dullness than does morphine; and it is relatively highly effective by oral administration.

The dose of Metopon is 6.0 to 9.0 mg. repeated only on recurrence of pain and avoiding regular by-the-clock administration. It is most desirable to keep the dose at the lowest level compatible with adequate pain relief. At present this drug is marketed in the United States by Sharp and Dohme, Inc. and by Parke, Davis and Co. and is to be used for the relief of pain in cancer cases only.

Methadon

Methadon is the generic term recognized by the Council on Pharmacy and Chemistry of the American Medical Association for

the drug known chemically as 6-dimethylamino-4,4-diphenyl-3-heptanone. The structural formula is:



Since Methadon is a synthetic morphine substitute its availability is always assured. It was first synthesized and called amidone by I. G. Farbenindustrie in Germany. It is a white crystalline substance, soluble in water and alcohol but insoluble in ether and has a bitter taste. A comparison of Methadon with morphine showed that 10 mg. of it are therapeutically equivalent to 15 mg. of morphine. It is indicated for the control of pain and discomfort following surgery, in renal colic, in metastatic lesions of malignant tumors, in distress of congestive heart failure and angina pectoris, in aortic aneurysm, in discomfort in poliomyelitis and in control of cough in various conditions. It does not completely relieve labor pains and has a tendency to produce neonatal asphyxia. It was not too effective as a preanesthetic medication. Various side effects have been noted such as nausea, vomiting, lightheadedness, drowsiness, dryness of the mouth, diaphoresis, mental depression and miosis (following large doses and much less pronounced than with morphine). The dose of this drug varies from 2.5 mg. to 10 mg. dependent upon the severity of the pain. It may be administered orally or subcutaneously.

Methadon is available from Eli Lilly and Co. as Dolophine; from Abbott Laboratories as Methadon Hydrochloride; and from Winthrop Stearns Inc. as Adanon.

AN 148

Another new analgesic agent which is being tried is 1-dimethylamino-3,3-diphenyl-2-methyl-4-hexanone and known as AN 148. It has been found to relieve pain satisfactorily in all but 4 of 106 patients suffering from a wide variety of diseases. As a pre-

anesthetic medication before both local and general anesthesia it has shown good results. The average intravenous dose is 5 mg. which is considered the equivalent of 15 mg. of morphine sulfate. No serious side effects have been noted. This drug is being studied by Abbott Laboratories.

Salicylamide

The search for new, non-opiate analgesics has led to the investigation of many types of compounds but has more or less bypassed the salicyl compounds, possibly because of their low water-solubility. However, recent investigations have been made of the analgesic properties of salicylamide and some of its derivatives and have shown them to equal or exceed the analgesic potencies of the already established analgesic-antipyretic drugs. On repeated administration salicylamide appears to be less toxic than acetylsalicylic acid. On the basis of the experimental work it is thought that more attention should be directed to these compounds.

Cytochrome C

Cytochrome C is an enzyme which has been found to play an important role in controlling tissue oxygenation. It is a protein which is normally present in all living tissues, animal or plant. Improvement has been noted when Cytochrome C was used in angina pectoris, Raynaud's disease, pulmonary emphysema, barbiturate poisoning, degenerative diseases associated with arteriosclerosis and certain cerebral dysfunctions. In cases of angina pectoris improvement has been so great that incapacitated patients were again able to get about. When the body tissues are not receiving sufficient oxygen from without, a supply of oxygen still remains in the blood and Cytochrome C makes it possible for this oxygen to be utilized. Humans placed in pressure chambers from which the air has been partially pumped suffer from impaired vision and thinking just as aviators do at high altitudes. Cytochrome C has been found to improve this condition. The possibility that mental deterioration due to hardening of the arteries may be aided has been suggested, as well as migraine and epilepsy headaches.

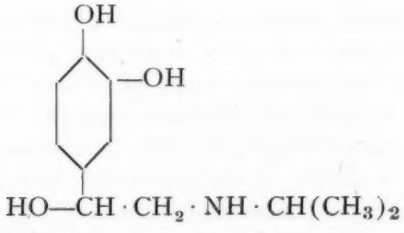
Cytochrome C is available for clinical trial from Schering Corp. and Viobin Corp.

Khellin

Khellin is the active principle of a plant, *Ammi visnaga Lam.*, which grows wild in Arabia and Eastern Mediterranean countries. For centuries this plant has been a popular remedy in Egypt for renal and intestinal colic. Now it has gained prominence as a coronary vasodilator which does not reduce blood pressure or increase the pulse rate. Chemically the active principle is a dimethoxymethyl-furano-chromone. It appears to act directly on the muscle fibers of the blood vessels and the selective response by the coronary vessels is believed due to their particular sensitivity. Encouraging results have been obtained in the therapy of over 150 patients suffering from various conditions such as angina pectoris, coronary thrombosis and bronchial asthma. The drug is given orally in doses of 40 mg. three times a day or intramuscularly in doses of 90 mg. daily or 120 mg. on alternate days. In bronchial asthma larger doses may be necessary. Full effect of the drug is achieved in one to three days. Further investigation of this drug is being made in respect to its clinical value as well as to its purification and standardization.

Isuprel

Known in Europe as aleudrin, Isuprel is an analogue of epinephrine and chemically is α-(3,4-dihydroxyphenyl)-β-isopropylamine ethanol.

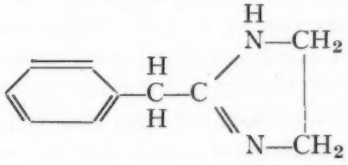


It is also known as isopropyl epinephrine and is similar to epinephrine in action. It is superior to the latter in its bronchiospasmolytic activity. In acting on the circulation it does not elevate the blood pressure but rather lowers it, due to the dilatation of the peripheral vessels. Undesirable side effects and tachycardia are minimal. The drug is administered orally, subcutaneously or by oxygen-aerosolization, never intravenously. Alarming reactions may occur if more

than 0.5 cc. of a 1:1000 solution is given subcutaneously. The dosage by inhalation is 1.0 cc. of a 1:100 dilution every 3 hours; by subcutaneous method, 0.20 to 0.33 cc. of 1:1000 dilution; and by mouth, 30 to 90 mg. daily. No addiction has been noted. The drug possesses great possibilities in the management of the chronic asthmatic. Isuprel is under investigation by Winthrop Stearns Inc.

Priscol

Priscol hydrochloride is thought to have value as a vasodilator and sympatholytic agent. Chemically it is benzyl-imidazoline hydrochloride and is related to histamine and phenylethylamine.



This drug acts chiefly as a sympathomimetic in that it causes peripheral and coronary vasodilation; stimulates the heart and increases its output; and has an inhibitory effect upon the gastrointestinal muscles. It also acts in some respects like acetylcholine and like histamine and is an effective adrenolytic agent and sympathomimetic anti-pressor. Use of this drug in human therapy is under further investigation by Ciba Pharmaceutical Products Co. in the United States although it is available in England and Europe.

Metopryl

Metopryl is the name coined for an isomer of ethyl ether known as *n*-propyl methyl ether, with the formula:

$$CH_3—O—CH_2—CH_2—CH_3.$$

It possesses an anesthetic effect 25 per cent greater that that of ether and has no harmful effects on the heart, liver or circulation. It is a volatile, colorless liquid with a pungent odor and a boiling point of 39°C. Its pungent odor does not allow for its use in open or semi-open systems. When used as an induction agent it is less offensive to the patient than is ether and it does not irritate the respiratory tract as much. However, it is not preferable to cyclopropane, Vinethene or nitrous oxide. Further work is necessary on

this compound to evaluate it completely. It is supplied by Ohio Chemical and Manufacturing Co.

Para-aminobenzoic Acid

Another war-research medical development is the use of para-aminobenzoic acid in the therapy of certain Rickettsial diseases such as typhus, spotted fever and tsutsugamushi disease. It appears to act as a rickettsiostatic agent rather than as a rickettsoicidal agent. It has been shown to inhibit the multiplication of the rickettsiae. In clinical use it is assumed that the immunity mechanisms of the host finally overcome the infection, the progress of which is arrested by the para-aminobenzoic acid. The drug is given orally or by intramuscular injection in doses varying with the disease and the patient. When the powdered acid is administered orally it should be given in a 5 per cent solution of sodium bicarbonate to prevent acidosis and nausea. If given as the sodium salt the bicarbonate is not necessary. Although para-aminobenzoic acid is not the sole answer in these conditions it is an important specific adjuvant along with proper supportive therapy. It is marketed as PABA and Sodium PABA by International Vitamin Division, American Home Products Corp. and by Wyeth Inc.

Pneumococcus Polysaccharides

Prevention of the most common types of pneumonia is now possible with the availability of a vaccine. A single subcutaneous injection of this immunizing agent builds resistance to the most prevalent types of pneumococcal or lobar pneumonia. Immunity usually develops within two weeks and is effective for at least a year. No adverse reaction has been observed from the vaccination. The vaccine is of no value in the treatment of a person already ill with pneumonia nor does it provide immunity against the virus pneumonia. The vaccine is a solution of the polysaccharides of the pneumococci. It is produced from the capsule surrounding the organism. This capsule consists of a viscous sugar-like substance which chemically is polysaccharide. Injection of this substance produces the protective antibodies. Of the 75 types of pneumococcus isolated 11 are responsible for 75 to 80 per cent of all pneumococcal or lobar pneumonia. Six of the 11 are responsible for pneumonia in adults and the other 5 plus 1 of the adult group are particularly common in children.

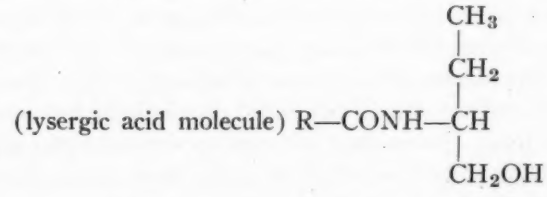
This vaccine has recently been made available as Solution of Pneumococcus Polysaccharides (Type-Specific) by E. R. Squibb and Sons. Combination A contains types 1, 2, 3, 5, 7 and 8 for adults and B contains types 1, 4, 6, 14, 18, and 19 for children. The dosage for adults and children over 12 years of age is 1 cc. subcutaneously injected, and for children under 12 the dose is 0,5 cc.

Hyperimmune Whooping Cough Serum

The only officially approved human serum for the treatment of whooping cough has recently been announced. It is manufactured from the blood of highly selected male donors in whom a high degree of immunization is built up. A whooping cough vaccine is injected into the donor and later a pint of blood is withdrawn and then processed into the serum. The immunization lasts for only a few weeks but is highly effective. It is stronger than other serums developed from individuals who have recovered from the disease. As a result of this serum the whooping cough death rate in children under six years of age has been reduced from 25 per cent to 8.2 per cent. The serum is available from the Serum Exchange of the Children's Hospital of Philadelphia where it was developed.

Methergine

Methergine, known chemically as *d*-lysergic acid-*dl* hydroxybutylamide-2, is a new synthetic ergonovine-like substance.



This compound has one more methylene group than ergonovine. It has a potent oxytocic action and has been used in labor. No toxic effects have been noted when administered either intramuscularly or intravenously. Administration of the drug effectively shortened the third stage of labor and reduced the postpartum blood loss. A rapid and more prolonged action on the uterus was observed when

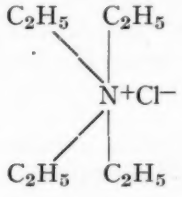
it was administered in doses of 0.2 mg. in 1 cc. of solution. Sandoz Chemical Works is supplying this drug for clinical trial.

Tantalum Oxide

In previous articles mention was made of the use of the element tantalum in surgery. A new development in this field is the use of tantalum oxide type 400 as a dusting powder in surgery. It is nontoxic and chemically inert and therefore can be used instead of gauze and sterile vaseline gauze in surgical wounds. The powder is thought to absorb blood, lymph or tissue juice and forms a crust and thus accelerates healing. This powder is prepared by the Fansteel Metallurgical Corp.

Etamon

Tetraethylammonium chloride is a quaternary ammonium compound with the following structure:

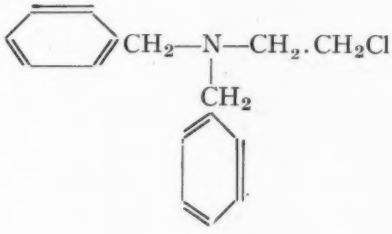


It acts by blocking the transmission of both sympathetic and parasympathetic nerve impulses at the autonomic ganglia. As a result of this block the arterial blood pressure falls due to vasodilation and there occur mydriasis, inhibition of gastrointestinal movements and function of other autonomically innervated structures. In some cases mild toxic effects have been noted particularly following intravenous injection. The average intravenous dose of a ten per cent solution (100 mg. per cc.) is 1 to 5 cc. The larger dose provides a more prolonged effect. For intramuscular administration the dose should not exceed 20 mg. per Kg. of body weight. This method produces effects lasting for 6 to 8 hours. Since acetylcholine and epinephrine act on the autonomically innervated structures at a point peripheral to the ganglia they counteract the effects of the tetraethylammonium ion on these structures and consequently can be used as antidotes if necessary.

Clinical study has been conducted with this drug on diseases in which a high degree of sympathetic nervous system tone may exist. Among such conditions are included the following: essential hypertension, functional and organic vascular diseases such as Raynaud's, acrocyanosis, livedo reticularis, thrombo-angiitis obliterans (Buerger's), peripheral arteriosclerosis, causalgia, thrombophlebitis, and reflex sympathetic dystrophy. Tetraethylammonium chloride is supplied in a 10 per cent aqueous solution, pH 6.48, with Phemerol 1:10,000 as a self-sterilizing agent under the name Etamon by Parke, Davis and Co.

Dibenamine

Another adrenergic blocking agent recently reported is dibenzyl-β-chloroethylamine which is structurally related to the nitrogen mustards and has the following formula:



It is effective when administered orally, subcutaneously, intramuscularly or intravenously. Large intravenous doses can be tolerated without local tissue damage and central excitation when the drug is slowly administered along with a sedative. It is thought that this compound may prove a useful tool for the study of the function of the sympatho-adrenal system and as a therapeutic agent in blocking the effects of this system. It may prove useful in a number of clinical states such as in peripheral vascular diseases where there is a component of functional spasm. In such cases it might be used to block the effects of sympathetic vasoconstrictor impulses. Interruption of sympathetic nerve impulses also causes favorable response in Raynaud's disease, causalgic states, early Buerger's disease and the vascular spasm which accompanies embolism and thrombophlebitis. Specific studies on cases of Raynaud's disease have shown a definite and prolonged salutary effect.

Hypertension caused by hyperfunction of the sympatho-adrenal system might possibly be helped by such an agent. Variable but encouraging results have been attained with it in the treatment of human essential hypertension. An initial transient orthostatic hypotension and a more prolonged lowering of the blood pressure have been noted. The prolonged action gives it an advantage over paravertebral local anesthetic block and ganglionic block with tetraethylammonium compounds. Sympathectomy is less advantageous due to the fact that this agent acts on all vascular beds, is not sensitized to epinephrine or sympathin and maintains intact any vasodilator fibers which may be present. In surgical resection its controlled reversibility is a distinct advantage.

Clinical trial on humans revealed that the safest method which showed more consistent results was the intravenous route. Orally the compound was poorly tolerated and results were unpredictable. The dose found to be effective was 4 to 6 mg. per Kg. of body weight given intravenously. The activity reached a peak within 24 hours. In some cases the response to standard sympathetic stimuli is affected for several days after the first injection.

This drug is supplied as Dibenamine for clinical trial by Givaudan-Delawanna, Inc.

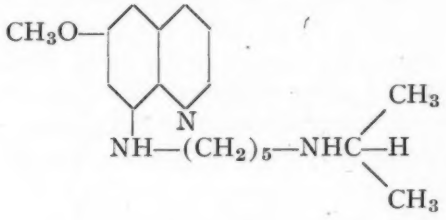
Nitrogen Mustards

Another war-encouraged research project has given evidence of helping mankind. The nitrogen mustards, methyl-*bis* (β-chloroethyl) amine hydrochloride and *tris* (β-chloroethyl) amine hydrochloride, have been found to possess therapeutic value in the treatment of Hodgkin's disease, lymphosarcoma, leukemias and other neoplastic conditions. They are not considered cures for the diseases studied but improvement has been noted following their careful administration. Optimal dosage schedules have not been established. Caution must be employed in using them since the margin of safety is very narrow.

Certain side effects such as pain on injection, thrombophlebitis of the injected veins, nausea, vomiting, malaise, anorexia and headache, may be encountered but can sometimes be avoided by careful technic. Leukopenia, granulocytopenia, thrombocytopenia and anemia may occur later in treatment unless dosage is carefully controlled.

Pentaquine

Pentaquine is the generic name given by the Council on Pharmacy and Chemistry of the A. M. A. to the chemical compound 6-methoxy-8-(5-isopropylaminoamylamino)-quinoline which has been found useful in curing malaria due to *P. vivax*.



When used in conjunction with quinine this compound has been found to be a superior curative agent. It is administered in a daily dose of 60 mg. of the base or 80 mg. of the phosphate (not to be exceeded) with 2 Gm. of quinine. The total dose should be administered in divided doses every 4 hours for 14 days. Concurrent administration of quinine increases plasma concentration of the pentaquine. Toxic effects noted include anorexia occasionally, abdominal pain and a slight methemoglobinemia. This drug is not released for general use.

Metachloridine

Field trials in British Guiana have shown that Metachloridine or 2-metanilamido-5-chloropyrimidine is the most active of metanilamide derivatives in suppressing natural infections of *P. malariae* and in partially suppressing parasitemia with *P. falciparum*. The dosage employed was 1 to 2 grams weekly, divided into 2, 3 or 5 parts. Good suppression of *P. vivax* was observed in a limited number of tests. During the 6 month period of therapy no toxic effects were noted. Further investigations are being carried out on lower and higher doses in the different conditions. This chemical is being investigated by American Cyanamid Co.

Diramin

Granuloma inguinale, a tropical disease, is an ulcerating tumor or neoplasm made up of granulation tissue. It affects the genitals and neighboring parts of the body. The usefulness of antimonial

preparations in the treatment of this condition has been established. A new antimonial has recently been developed and shows promise in the therapy of this disease. This new compound is an aqueous solution of the reaction mixture resulting from the reaction between antimony catechol and triisopropanolamine in the presence of propylene glycol. It contains 8.17 mg. of antimony per cc. and is administered in 2 cc. doses 2 to 5 times per week without untoward side reactions. Pain and local irritation were noted with intramuscular injections. A series of clinical trials have shown that this compound is a good, safe preparation for the therapy of *granuloma inguinale*. It is available for clinical trial as Diramin from Parke, Davis and Co.

Diamidines

Considerable therapeutic value in the treatment of a number of protozoal and bacterial diseases has been demonstrated by three diamidine compounds which include 4:4′-diamidino stilbene or Stilbamidine; 4:4′-diamidino-diphenoxy pentane or Pentamidine; and 4:4′-diamidino-diphenoxy propane or Propamidine. These compounds have shown a species rather than a class specificity against trypanosomes since *T. rhodesiense* and *T. congolense* infections were helped whereas *T. cruzi* infections were not. Considerable activity was exhibited against human leishmaniasis which is common to the tropics and is exceedingly dangerous. Promising effects have been noted in the therapy of human trypanosomiasis. Treatment with the diamidines of infections of surface wounds such as in burned surfaces and in wounds associated with plastic surgery showed that they possess bactericidal power against streptococci and staphylococci. Transient side effects which included flushing of the face, epigastric discomfort, rapid pulse, headache, sweating, retching and occasional vomiting were noted with doses in excess of 1 mg. per Kg. of body weight. The symptoms disappeared within half an hour and frequently failed to appear after further injections. Occasional fatalities have occurred although the compounds appear to be relatively safe.

Stilbamidine appears to be more effective than Pentamidine in leishmaniasis and more effective in the early stages of trypanosomiasis than in the later. No effect was noted in rheumatoid arthritis. Tests have also been made with Stilbamidine and Pentamidine in the treatment of multiple myeloma. Some favorable effects were

noted with Stilbamidine and there appears to be some connection between the metabolic aspects of multiple myeloma and the influence of Stilbamidine. It is manufactured by May & Baker Ltd., Dagenham, England.

Histamine

Meniérès symptom complex is made up of 3 chief symptoms, vertigo, tinnitus and deafness. Many drugs have been investigated for their effectiveness in this condition but no one has been found which is ideal. Recent reports have shown that nonspecific histamine therapy is of some value.

The best results are obtained when the histamine is administered in an 0.8 per cent solution of potassium chloride. Histamine diphosphate, 2.75 mg., is dissolved in 250 cc. of the 0.8 per cent solution of potassium chloride and injected at the rate of 20 to 60 drops per minute. Physiological salt solution or 5 per cent dextrose solution may also be used as vehicles. This quantity is equivalent to 1 mg. of histamine base. The blood pressure and pulse rate should be checked frequently while administering the drug. This dosage is given for 3 to 6 days. Concurrent with this or following it a 1:10,000 solution of histamine base is subcutaneously administered in doses of 0.2 cc. increased by 0.05 cc., twice a day, up to 1.0 cc. or until the optimal dose is attained. The daily injections are continued and gradually diminished according to the patient's response. In severe cases intravenous injections may be necessary for several days. In order to prevent an attack of vertigo it may be necessary to administer histamine intravenously during the subcutaneous desensitization. Histamine has also shown some value in sudden nerve deafness.

A C S

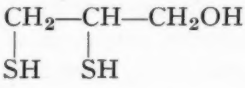
Within recent years a new branch of medicine has emerged. It is known as geriatrics and is concerned with old age. Some years ago Bogomolets concluded that the secret of long life is buried in the body so he began to investigate this. As a result there was announced in 1946 that antireticular cytotoxic serum (A C S) was of value in prolonging life. Unfortunately, as with many other achievements in medicine, the publicity on this serum exaggerated its effectiveness. It will not cure cancer and all forms of arthritis as was thought. Professor Bogomolets recommended that it be used immediately after the removal of cancer tumors so as to prevent their

recurrence. His statement that man should live to the age of 150 years was modified with the statement that this was possible if the serum is used when the connective tissues begin to deteriorate. It is also necessary for the person to have good food, exercise and maintain a sane way of living.

The serum is intended to stimulate the system of connective tissues, thus activating its defense against disease, increasing the resistance of tissues against infection and speeding the healing process in the development of tissue. The latter is where the serum is of benefit in cases of gastric ulcers. Thus the A C S helps to stop the degenerative processes which begin after middle life. It has also shown good results in the early states of arterial sclerosis but not in encephalitis. The serum is extracted from the blood of horses which have been injected previously with spleen cells and bone marrow of young, healthy individuals who died as a result of an accident. Experimental work on this compound has been carried out by Wyeth Inc.

Dimercaprol

Another development of war-inspired research is the use of dimercaprol or B A L (British Anti-Lewisite) in metallic toxicosis. Chemically B A L is 2, 3-dimercaptopropanol:



It was employed as a decontaminating and neutralizing agent against the deadly war gas "lewisite" from which use was derived its name. This compound acts by forming a relatively nontoxic and stable compound with the metallic radical. Arsenic and other metals readily combine with thiol groups. For this reason by offering this synthetic dithiol compound there is competition between it and the dithiol-containing proteins in the tissues for the arsenic. This also applies to other metals.

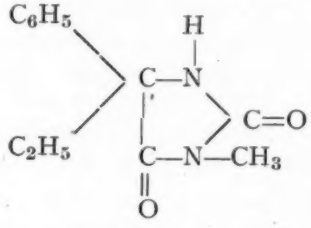
Dimercaprol consequently has been found of use in arsenic, gold, mercury and cadmium poisonings as an antidote. However, it has opened a new field of endeavor in respect to gold therapy. Gold compounds have been widely recommended as preferred in rheumatoid arthritis. Unfortunately due to the toxicity of these products as a result of cumulation in the tissues they have received only

limited usage. It has been suggested therefore that dimercaprol be used in conjunction with gold therapy since it causes an almost immediate reversal of toxic symptoms. If the side effects experienced with dimercaprol become too marked barbiturates may be given.

Dimercaprol (name adopted by Council on Pharmacy and Chemistry of A. M. A.) is marketed in a 10 per cent peanut oil solution as B A L-in-Oil by Hynson, Westcott and Dunning. Benzyl benzoate 20 per cent is added for stability. It is administered intramuscularly.

Mesantoin

Mesantoin is 3-methyl-5,5-phenyl-ethyl-hydantoin, a new anticonvulsant recently synthesized.



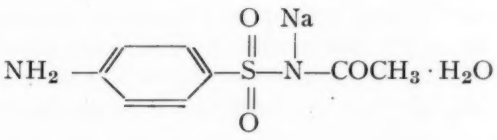
It owes its activity, of course, to the hydantoin portion of the molecule. It is indicated in grand mal and psychomotor equivalents of epilepsy. Side effects noted include drowsiness and a skin rash but these usually appear with large initial doses. By beginning with small initial doses desensitization may be produced. The average adult dose is 0.2 to 0.6 Gm. daily. This may be increased to 0.8 Gm. or more if necessary. Children usually react to a dosage of 0.1 to 0.4 Gm. The dosage is necessarily adjusted to the individual. Mesantoin (Phenantoin) is marketed by Sandoz Chemical Works.

Irradiation Technic

Vaccines are a problem to pharmacists because of their tendency to deteriorate even at refrigerator temperatures. Ultraviolet irradiation technic has been found to produce a vaccine which consistently induces a high degree of immunity and does not exhibit significant loss of potency after several months of storage. This technic is being applied by Parke, Davis and Co. and the first vaccine to be marketed under this process is rabies vaccine. The term Iradogen has been applied to this group of products.

Sodium Sulfacetimide

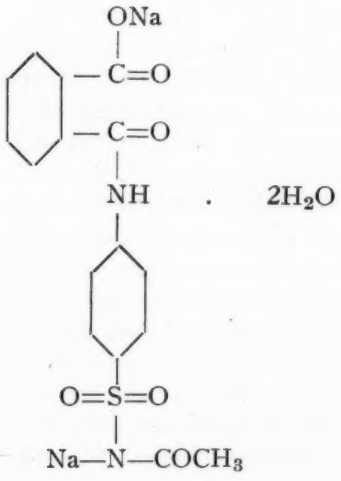
Chemically sodium sulfacetimide is N^1-acetyl-4-aminophenylsulfonamide with the following structural formula:



It is very soluble in water and is the only sulfonamide compound which can be used in high concentration at the physiologic pH of 7.4. It possesses high antibacterial activity and is non-irritating to mucous membranes. Sodium sulfacetimide has been used with excellent results in treating eye infections due to *Staphylococcus aureus* and *albus,* pneumococcus, gonococcus, hemophilus (Koch-Weeks) and numerous other organisms. Synonyms for this drug are sodium sulamyd, albucid soluble, and sodium *p*-aminobenzene-sulfonylacetylimide. Sodium Sulfacetimide Solution 30% and Ointment 10% are supplied by Schering Corp.

Sodium Phthalyl Sulfacetimide

Sodium phthalyl sulfacetimide, or disodium N^1-acetyl-N^4-phthalylsulfanilamide dihydrate has the following structural formula:



This sulfonamide compound has been shown to be an actively bactericidal compound with the unique property of being absorbable into the intestinal wall in high concentration although it is unabsorbable in respect to the blood stream.

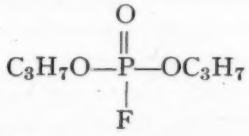
It exhibits the peculiarly low toxicity of compounds of the sulfacetimide series, as compared with the well-recognized toxicity of N^1 substituted sulfanilamides. Since it establishes a high effective concentration at the locus of infection proper, neither reaching it incidentally to a high level in the circulating blood nor approaching it superficially by virtue of simple admixture with the intestinal contents, it would be expected to display exceptional effectiveness in the treatment of enteric infections. It is of clear efficiency in reducing the ordinary bacterial flora, as in preoperative prophylaxis. Although it is not effective on all organisms, and other agents in some cases are more active, this compound has an advantage over the others in that equally effective concentrations can be brought to bear at the exact site of the infection.

Sodium phthalyl sulfacetimide is available in powder form and is dissolved in water for adults or in milk for young nursing infants. No dosage schedule has been developed but it is recommended that it not exceed 0.2 Gm. per Kg. of body weight in 24 hours. Much smaller doses are thought to be effective. It is indicated as a prophylactic in preoperative surgical preparation and as a chemotherapeutic agent in the active treatment of shigellosis and other enteric infections. Sodium phthalyl sulfacetimide is available for clinical investigation from Schering Corp.

Diisopropyl Fluorophosphate

A new drug, developed originally as a chemical warfare agent, has shown great value in glaucoma therapy. Glaucoma is a condition of the eye in which there is heightened intraocular tension. The cause of this disease is not definitely known.

Diisopropyl fluorophosphate, commonly known as DFP,



is a powerful inhibitor of cholinesterase. Therefore, it possesses parasympathomimetic and nicotinic actions. In inhibiting the cholin-

esterase, DFP combines with it and eliminates it from the reaction. This is in contradistinction to other inhibitors which when inhibition is completed, release the enzyme to continue its activity. Administered to the eye, DFP produces prolonged and marked pupil contraction, spasm of the ciliary muscle, false myopia, and a decrease in intraocular tension. No other miotic drug possesses such a prolonged action. DFP is antagonistic to homatropine and atropine.

DFP is an oily substance, miscible with oils, and relatively stable in peanut oil. It is not so stable in water. Therapeutically it is employed in concentrations of 0.05 to 0.1 per cent in oil. Although it is not effective in all cases of glaucoma, it is of definite value. Visual blurring, brow ache and eye ache, spasm of accommodation and pericorneal injection may occur as side reactions, thus eliminating its use in certain types of glaucoma.

Some of the uses in which DFP may be indicated are as follows: (1) DFP produces little discomfort in patients with glaucomatous, aphakic eyes, and it appears to be a most effective agent in controlling the tension of such eyes. (2) DFP is able to overcome the pupillary and accommodative effects of atropine. It should prove of therapeutic value in preglaucomatous and glaucomatous eyes unfortunately and inadvertently treated with atropine. (3) DFP may be helpful in controlling the tension in eyes in which operation must be postponed and pilocarpine or physostigmine has proved ineffective. (4) DFP properly may be used initially in relief of acute congestive glaucoma, since it is a more powerful agent than physostigmine. Being an anticholinesterase agent, it is believed that DFP can be used in eye conditions in which physostigmine formerly was employed. Due to its prolonged action, DFP has shown gratifying results in the treatment of postoperative ileus, and possibilities in myasthenia gravis.

Neo-Curtasal

There are many people who must have salt (sodium)-free diets and consequently they are constantly confronted with the problem of seasoning their foods. Several preparations for this purpose have been available for years. Recently a new one has been announced. It is an odorless, white, crystalline, somewhat hygroscopic powder, consisting of potassium chloride, ammonium chloride, potassium formate, calcium formate, magnesium citrate and starch with a taste

like sodium chloride. This compound is indicated for salt (sodium)-free diet in cardiac and renal diseases, particularly when associated with edema, hypertension, arteriosclerosis, certain complications of pregnancy, epilepsy and for Gerson diet in tuberculosis. It is supplied under the trade-name of Neo-Curtasal by Winthrop-Stearns, Inc.

Lycoyte Powder

Dried human blood cells when sprinkled in liberal quantity over an affected area, such as in wounds, minor burns and ulcers have been found to stimulate the growth of healthy granulation tissue and serve as a medium for the growth and extension of epithelial cells over the granulating surface. If a crust forms over the lesion with the powder this serves to support the growing connective and epithelial tissue beneath it. The powder which is prepared contains a small amount of residual plasma, the stroma and the contents of the acellular elements of the blood. Human blood cells prepared by the lyophile process are marketed as Lyocyte Powder Dried Human Blood Cells by Sharp and Dohme, Inc. This product is indicated as an aid in tissue regeneration to superficial and deep wounds and lesions such as varicose, decubitus and ischemic ulcers; open lesions of traumatic origin; potentially infected wounds such as second and third degree burns; deep abrasions and irregular lacerations; postoperative wounds, amputations, chest wounds and certain postoperative states.

Chaulmoogra Oil

For years chaulmoogra oil has been the accepted treatment for leprosy. Recently it was announced that this drug in conjunction with streptomycin produced striking results in the treatment of tuberculosis. The chaulmoogra oil dissolves the waxy coating on the tuberculosis bacillus thus making it more susceptible to the streptomycin. Streptomycin alone suppresses rather than kills the organisms and must be given in large doses with the then increasing possibility of toxic effects.

Pyriplex

Nausea and vomiting frequently are unpleasant complications of pregnancy. Many drugs have been used with moderate success in relieving this condition. Recently pyridoxine has been shown to be exceptionally effective despite the fact that the underlying cause of the condition is quite complex and involves physical, emotional

and psychological disturbances. Pyridoxine has also been found of value in irradiation sickness.

Pyriplex, marketed by the S. E. Massengill Co., contains pyridoxine hydrochloride, thiamine hydrochloride, riboflavin, nicotinamide, glucose and aromatics in a liquid vehicle. The glucose is included to provide carbohydrate of which there is a depletion and which is a factor in the etiology of the condition. The other vitamins are added to assure proper assimilation of the carbohydrate.

Nidoxital

Another preparation for the control of nausea and vomiting of pregnancy is in tablet form and contains benzocaine, pyridoxine hydrochloride, nicotinamide, *dl*-methionine and pentobarbital sodium. The pyridoxine hydrochloride is necessary for proper fatty acid utilization, as well as helping to maintain normal nerve function, normal erythropoiesis and is necessary in larger quantity where body metabolism is increased. Nicotinamide reduces the peristaltic action of the stomach and small intestine therefore decreasing excitability. The *dl*-methionine tends to prevent cumulative liver damage. Benzocaine as a local anesthetic acts on the peripheral nerve endings and decreases efferent excitation to inhibit transmission of impulses to the vomiting center. The barbiturate, pentobarbital sodium, depresses the vomiting center by its action upon the central nervous system. This product is available as Nidoxital from Ortho Pharmaceutical Corp.

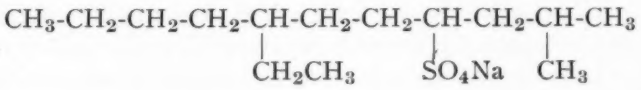
Argypulvis

A new product has been developed which extends the use of mild silver protein (Argyrol) to other fields. This product is particularly designed for use in the vagina in the treatment of *Trichomonas vaginalis* vaginitis. The product is bacteriostatic, fungistatic, protozoicidal and demulcent and contains in addition to 20 per cent of mild silver protein, 40 per cent each of kaolin and beta lactose. It is supplied under the name Argypulvis by A. C. Barnes Co.

Sotradecol

The treatment of varicose veins has always provided a complex therapeutic problem. For the permanent obliteration of such veins, it is necessary to produce a firm and adherent thrombus and then to protect it from excessive hydrostatic pressure for an extended period of time.

Research into various compounds has shown that sodium tetradecyl sulfate or 2-methyl-7-ethylundecyl-4-sulfate is of value in the treatment of this condition. The structural formula for this compound is:



A 3 per cent solution is the equivalent in effectiveness of a 5 per cent solution of the strongest soap type sclerosing agent. Sodium tetradecyl sulfate is supplied in 1, 3 and 5 per cent solutions with 2 per cent benzyl alcohol under the name of Sotradecol by Wallace and Tiernan Products, Inc. This compound produces a penetrating but not diffused irritating action on the intima of the veins. When injected subcutaneously it does not cause inflammation, sloughing or necrosis. A well-demarcated necrosis with a minimum of inflammation will be noted if it is injected intradermally.

Thymine

Thymine is a part of nucleic acid and received its name from the fact that it was first isolated from the thymus gland. Now it is synthesized. Thymine possesses effects similar to folic acid in Addisonian pernicious anemia and nutritional macrocytic anemia of pellagra, pregnancy and sprue. However, much larger doses of thymine are necessary. Within three or four days after therapy is instituted the arrested red blood cells form large islands of regeneration and pass into the blood in great numbers.

Methionine

dl-Methionine is an amino acid which has shown some therapeutic promise in the prevention and treatment of liver injury caused by poisons such as arsenic, chloroform, carbon tetrachloride, anasthetic gases and others. It has also been suggested for treating cirrhosis of the liver, infectious hepatitis, eclampsia and shock. Further investigation is being conducted in substantiation of these possible uses. Methionine is marketed as such by the National Drug Co. and Walker Vitamin Products and as Meonine by Wyeth, Inc. The oral dosage is 2 to 4 grams daily.

Hydrosulphosol

Sulfhydryl pentathionate has been found to act as an epithelial stimulant and as such is of use in burn therapy. Incorporated into the product Hydrosulphosol, sulfhydryl pentathionate presents sulfur in a free colloidal form with a high concentration of sulfhydryl. Thus it is thought that sulfur is available in a form which is utilizable by the body in the synthesis of sulfur-containing amino acids. Application of this substance to an injured area deposits a thin layer of sulfur or calcium and during the process of forming a coating sulfhydryl or sulfur is absorbed by the body. The coating should be maintained in a thin pliable layer.

In addition to skin burns this compound is particularly valuable in eye burns. A dilution of 1:40 (pH 8.2) in warm triple distilled water is dropped into the eyes every 30 minutes to 2 hours dependent upon the extent of injury and other factors. Compresses of a 1:20 dilution (pH 8.5) in warm distilled water should be applied to the outside of closed lids continuously for several hours. Concentration of the solution by evaporation will produce a concentrate which can be incorporated into a cold cream base for use on areas outside of the eye. This product in conjunction with penicillin in multiple corneal ulcers produces better results than penicillin alone. No toxic reactions or contraindications have been noted. Hydrosulphosol is marketed by Rees-Davis Drugs, Inc.

Urethane

Ethyl carbamate has been reported to have a palliative effect in cases of myeloid or lymphatic leukemia in humans. It has been shown to retard the growth of certain neoplasms although such alteration was not permanent. Relapses took place and immature cells reappeared in the blood. However it does show possibilities and opens a new field of investigation.

Hemokin

Recent literature has shown that menadione (vitamin K) is of value in counteracting the possibility of hemorrhage in salicylate therapy. This is particularly of value in conditions such as rheumatic fever and gout where extensive salicylate therapy is used. For this reason acetylsalicylic acid and menadione have been combined in one preparation.

Hemokin, Winthrop Chemical Company's product, contains 0.3 Gm. of acetylsalicylic acid and 0.3 mg. of menadione in each tablet. This product is also indicated as an analgesic in neuralgic and muscular pains, headache, migraine, head colds and after tonsillectomy and adenoidectomy. Lakeside Laboratories have available Menacyl which contains acetylsalicylic acid 0.33 Gm., menadione 0.33 mg., and ascorbic acid 33.3 mg.

Meprane

A new synthetic estrogen, 3,4-bis-(*m*-methyl-*p*-propionoxyphenyl) hexane has been made available for oral administration in the menopausal syndrome and in other clinical manifestations of hypoestrinism amenable to estrogenic therapy as well as in suppression of lactation. Because of its potency only a relatively low dose is necessary and the drug is well tolerated. Reed and Carnrick are marketing this drug under the name Meprane.

Diphtheria, Tetanus and Botulism Toxoids

Pure diphtheria toxoid was isolated early in 1947. This marks a great advance in this form of therapy since it can now be used in persons of all ages without side reactions. The crude diphtheria toxoid could be used only in very young children without experiencing unpleasant side reactions. One ounce of the pure form will protect 400,000 persons.

The Institute of Pathology of Western Reserve University, in addition to isolating the diphtheria toxoid, also recently isolated the toxin of tetanus. U. S. Army chemists have also announced the isolation of the toxin of botulism. Great advances are being made in this field.

Multiple Injection Products

Three antigens are now being combined in one vial so as to simplify the immunization of children. These combinations include diphtheria, pertussis and tetanus, thus allowing for a single injection rather than three. It is hoped that in the future scarlet fever and typhoid will also be included. The advantages of this method are obvious.

Diopterin and Teropterin

A recent announcement stated that two new synthetic substances were being tested in retardation of cancer in humans. Although not believed to be cures, enough change has been shown to justify further tests. Pteroyl diglutamic acid or Diopterin and pteroyl triglutamic acid or Teropterin, derivatives of folic acid, are the chemicals being tested by Lederle Laboratories. For the first time the cancer problem has been approached from a nutritional standpoint. The substances are administered intravenously or intramuscularly and it may be several weeks before effects are noted.

Hypospray Gun

A new development shortly to be released is a Hypospray Gun for needle-less injection of parenteral medicaments. This new process is painless, easy to use and leaves no visible mark on the skin. This new apparatus is being tested by the R. P. Scherer Corp.

Hormones in Cancer

Recent reports of the use of testosterone propionate and estrogen in the therapy of breast cancer have been published. Although neither method of treatment assures a permanent cure as yet, a new field of investigation has been opened.

Testosterone propionate is believed to exert a favorable influence on advanced carcinoma of the female breast. When administered in large doses (50 mg. daily or 100 mg. every other day) over a twelve-week period either by injection or by subcutaneous implantation, pain from cancer of the bone was relieved quickly and a bony deposit was formed over the destroyed areas of the bone. The primary lesion and the soft part metastases regressed and in some cases the bedridden patient was back at work within a month.

Estrogen was found to be effective in women above 60 years of age in influencing a reduction in the mass of cancer in the breast toward a complete elimination of the disease, as well as other beneficial results. Ethinyl estradiol and stilbestrol are the estrogens used. They have also shown value in the treatment of cancer of the prostate.

Testosterone propionate is sold as such by Rare Chemicals Inc. It is available as Perandren from Ciba Pharmaceutical Products Inc.,

as Neo-Hombreol from Roche-Organon Inc., and as Oreton from Schering Corp.

Ethinyl estradiol is marketed under that title by Ciba Pharmaceutical Products Inc., as Lynoral by Roche-Organon Inc. and Estinyl by Schering Corp. Many companies market stilbestrol.

Fibrin Film

The newest product of the blood fractionation process to be made available is a film made entirely of the coagulating elements of human blood. It may be left in the body without causing any inflammation. It is uniformly thin, smooth, sheet-like and is soaked in sterile saline solution before using. After soaking it becomes elastic similar to a moist tissue membrane. This substance is used in brain and plastic surgery, and as a dressing for burns. In the brain it is used to cover the damaged brain or spinal cord where it eventually becomes vascularized and forms a permanent neoplastic membrane. In burns and plastic surgery it prevents drying and adhesions and may be removed without damage to the healing area underneath. Fibrin Film was recently introduced by Cutter Laboratories.

Antibiotics

Several new antibiotics have been discovered recently, among which are included Aerosporin, colistatin, erythrin, litmocidin and two from wild ginger. Aerosporin has been shown to be bactericidal to the Gram-negative *Hemophilus pertussis, Eberthella typhosa* and *Escherichia coli* in the field of human medicine and *Brucella bronchiseptica and Escherichia coli* strains of calf scour in veterinary medicine. Colistatin is a bacteriostatic agent and has shown some effect against staphylococci, pneumococci, *B. coli, B. proteus, B. paratyphosus B., B. dysenteriae Shiga* and *B. typhi abdominalis.* Erythrin, discovered by the Russians, has shown effectiveness against diphtheria. Litmocidin is bacteriostatic and bactericidal to most strains of staphylococci, streptococci, and vibrio comma. Two antibiotic substances, A and B, have been isolated from wild ginger (*Asarum canadense*). A has been found to be active against the pus forming Gram-positive bacteria, staphylococcus, streptococcus and pneumococcus but has no effect on intestinal bacteria. B has less activity.

All of these antibiotic agents require more extensive investigation before any definite statements as to their value in therapy can be made.

Another product of tyrothricin was recently released by Sharp and Dohme Inc. Tyrozets are antibiotic and anesthetic throat lozenges indicated in the treatment of mouth and throat infections due to Gram-positive organisms. They are also useful following tonsillectomies. The benzocaine present soothes irritated tissues and relieves irritation. Each lozenge contains 1 mg. of tyrothricin and 5 mg. of benzocaine. One is to be dissolved slowly in the mouth every 3 hours.

Various improvements in penicillin have been made, such as the crystalline potassium salt of penicillin G by Commercial Solvents Corp. This salt is high in purity, heat stable and does not require refrigeration. In patients with certain types of heart disease and Bright's disease, who have a limited tolerance to sodium, the potassium salt is particularly advantageous.

The announcement of the synthesis of benzylpenicillin was another striking advance. Although nowhere near a production basis it promises new horizons.

New developments have gained prominence in streptomycin therapy as well. It has shown great promise in the treatment of certain urinary tract infections and possibilities in tuberculosis. The preparation of the Calcium Chloride Complex of Streptomycin by Merck and Co. has provided a more pure product as well as one with uniform potency, decreased toxicity and one which gives minimum pain on injection.

One of the problems with penicillin and streptomycin is the rapid excretion, making it necessary to give large and frequent doses. Recently it was shown that pectin was found to slow down this rate of excretion. A 0.5 Gm. dose of streptomycin was maintained for 48 hours. Further studies are being carried on, as well as studies on the effect of pectin with other drugs such as ephedrine, epinephrine and insulin.

A new product, which blocks the kidney tubules and holds the penicillin in the body longer, was recently announced. Known as caronamide, this synthetic substance chemically is 4′-carboxyphenylmethanesulfonanilide. Penicillin is also excreted through glomerular filtration, but by blocking the renal tubules only about 20 per cent of the drug is excreted at the normal rate. The drug used for this purpose of course must be nontoxic and not affect any other kidney mechanism. Caronamide appears to compete for the enzyme through

which penicillin excretion is effected. This compound when administered with penicillin in clinical trials has shown remarkable results in all penicillin-sensitive organism-caused infections and particularly in gonorrhea. It is available as Staticin Caronamide from Sharp and Dohme Inc.

Penicillinase is a laboratory reagent which inactivates penicillin. It is a type of enzyme and is used in making cultures of body fluids from patients being treated with penicillin. Penicillin levels in the body fluids of these patients may inhibit the growth of the infecting organism if still present. Thus a test with penicillinase limits the possibility of false negative cultures. When added to the culture before incubation it destroys penicillin within an hour and permits the remaining bacteria to grow. Penicillinase is marketed as a dry powder by Schenley Laboratories Inc. One unit is that quantity which in 11 ml. of pH 7.0 solution containing 50 Oxford units of penicillin will destroy in 1 hour at 37°C. an amount of penicillin equal to 57.5 per cent of the penicillin recovered in control.

Hyaluronidase

Hyaluronidase is an enzyme prepared from bovine testes and other sources which possesses the property of hydrolyzing hyaluronic acid, one of the polysaccharides found in the intercellular ground substance of connective tissue and a constituent of certain specialized materials such as the vitreous humor and umbilical cord as well as some micro-organism such as in the capsules of A and C hemolytic streptococci. It is a spreading factor and occurs as a protein or closely associated with a protein. Hyaluronidase has been tested for its effectiveness in various conditions. Most striking results have been achieved with it in hypodermoclysis and infertility. In the former a preliminary injection of 10 to 20 micrograms of hyaluronidase in 1 to 2 cc. of saline accelerates the absorption of hypodermically administered fluids, such as 5 per cent glucose in physiological saline. The enzyme is injected at the site and hypodermoclysis is begun without withdrawing the needle. It may also be injected into the tubing.

The effect lasts for about 24 hours, and consists of a marked increase in the rate at which the fluid is taken up by tissues having such elasticity as to render the inflow and uptake of fluid unduly slow; in lax, dehydrated tissues the absorption, already rapid, is not

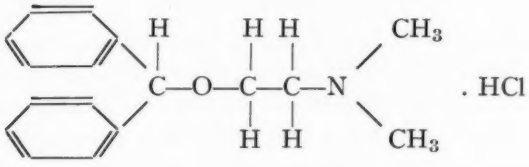
greatly increased. It is suggested that such an accelerated clysis might be of advantage for administering saline, and even plasma, in cases where intravenous therapy is difficult and large amounts of fluid are desirable with a minimum of delay.

In infertility hyaluronidase has been shown to play a physiological role in the fertilization of the ovum by dispersion of the corona cells. It may be added to the semen before artificial insemination or applied to the cleaned cervix shortly before coitus.

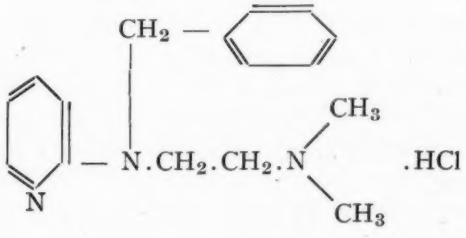
Hyaluronidase is available for clinical investigation from Schering Corp.

Antihistaminics

Many antihistaminics have been developed in recent years for therapy of allergic and related conditions. The first to be commercially available and which is now well known is Benadryl marketed by Parke, Davis and Co. Chemically it is beta-dimethylamino-ethylbenzohydryl ether hydrochloride:

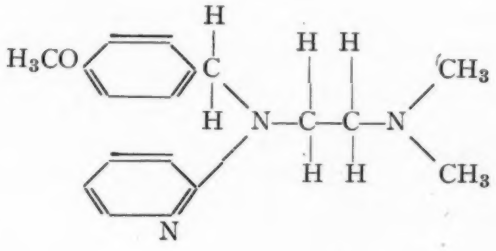


Pyribenzamine Hydrochloride is marketed by Ciba Pharmaceutical Products Co. and chemically it is N′-pyridyl-N′benzyl-N-dimethylethylenediamine hydrochloride.

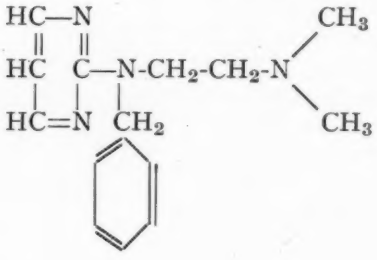


It is also known as diaminobenzopyryl and as Tripelennamine Hydrochloride, N. N. R.

Neoantergan, first described in France, is being investigated by Merck and Co. Chemically it is N-*p*-methoxybenzyl-N-dimethyl-aminoethyl-α-aminopyridine:

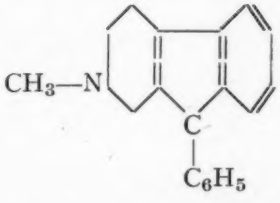


Hetramine is N,N-dimethyl-N′benzyl-N′ (α-pyrimidyl) ethyl-enediamine and is being tested by Pyridium Corp.

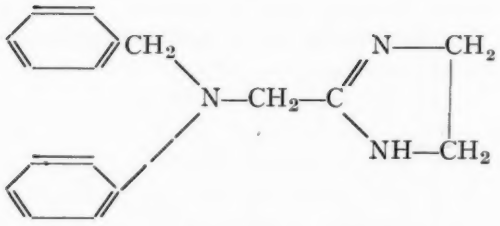


Hydryllin, recently released by G. D. Searle and Co. is a combination of 25 mg. of diphenhydramine and 100 mg. aminophyllin.

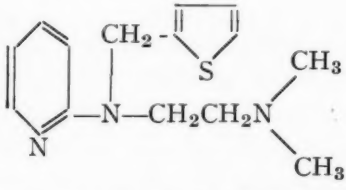
Thephorin or 2-methyl-9-phenyl-tetrahydro-1-pyridindene is available for clinical trial from Hoffmann La Roche Inc.



Antistin is marketed by Ciba in England and Europe. Chemically it is 2-(phenyl-benzyl-aminomethyl)-imidazoline.

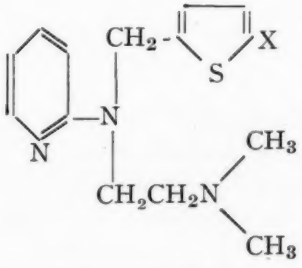


Thenylene, being investigated by Abbott Laboratories and Histadyl by Eli Lilly and Co. and W53 by Wm. R. Warner and Co. have the following formula:

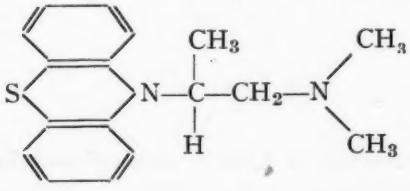


Chlorophen and Bromophen are being tested by American Cyanamid Co.

X = Br, Cl



3277 RP is a Rhone-Poulenc compound with the following formula:



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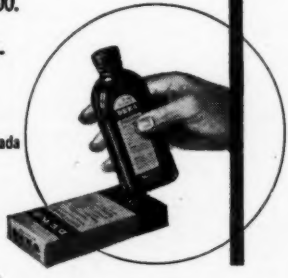

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SODIUM IODIDE
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IODOCHLOROHYDROXYQUINOLINE TABLETS
IODOFORM
POTASSIUM IODIDE SOLUTION
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American Journal of Pharmacy

The American Journal of Pharmacy is the oldest continuously published scientific periodical of its kind in America, having been established by the Philadelphia College of Pharmacy in 1825. After the original issue there were three other preliminary numbers until 1829, when regular publication began. From then until 1852 four issues were published annually, with the single exception of 1847, when an additional number appeared. Six issues a year were printed from 1853 to 1870, at which time the Journal became a monthly publication.

Former Editors of the Journal have been: Daniel B. Smith, 1825-1828; Benjamin Ellis, 1829-1831; Robert E. Griffith, 1831-1836; Joseph Carson, 1836-1850; William Procter, Jr., 1850-1871; John M. Maisch, 1871-1893; Henry Trimble, 1893-1898; Henry Kraemer, 1898-1917; George M. Beringer, 1917-1921, and Ivor Griffith, 1921-1941.

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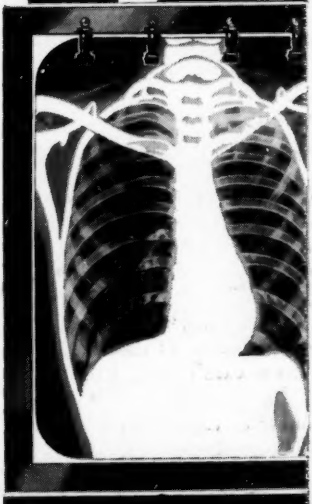

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